The impact of the introduction of bortezomib on dialysis independence in multiple myeloma patients with renal impairment

Oortgiesen, Berdien E; Azad, Roshna; Hemmelder, Marc H; Kibbelaar, Robby E; Veeger, Nic J G M; de Vries, Joost C; van Roon, Eric N; Hoogendoorn, Mels

Published in:
Haematologica

DOI:
10.3324/haematol.2017.184754

Publication date:
2018

The impact of the introduction of bortezomib on dialysis independence in multiple myeloma patients with renal impairment: a nationwide Dutch population-based study

The proteasome inhibitor bortezomib has a positive effect on renal function in multiple myeloma (MM) patients with renal impairment (RI).[1-3] This led to an update of the Dutch and international guidelines in 2010, recommending bortezomib as first-line treatment in patients with RI.[1,4] Our results show that the number of patients becoming dialysis independent increased more than twofold and more rapidly in the first year of dialysis treatment after the establishment of bortezomib as first-line treatment in MM patients with RI. Age <75 years and MM nephropathy without amyloidosis were associated with achieving dialysis independence.

RI in MM patients occurs in 20-50% of patients at diagnosis and is associated with poor survival.[5-7] Approximately 10% of these patients require dialysis.[8] Myeloma cast nephropathy (MCN) is the most common type of renal injury in MM patients, other causes are amyloid light chain amyloidosis (AL amyloidosis) or light chain deposition disease (LCDD).[9] Few studies evaluated the effect of bortezomib in dialysis-dependent MM patients.[10,11] We determined the effect of the guideline introducing bortezomib as first-line treatment in dialysis-dependent MM patients on becoming dialysis independent. *Online Supplementary Figure S1* highlights changes in first-line treatment in the Netherlands.

We included patients on chronic renal replacement therapy (RRT) (renal transplantation or dialysis treatment >28 days) registered in the nationwide Dutch renal registry Renine between January 2002 and January 2016. Patients are coded as MM nephropathy without proven amyloidosis (MCN or LCDD) or as confirmed AL amyloidosis. Every Dutch dialysis center is obliged to provide data regarding age, gender, start date of RRT, type and switches of RRT or hospitals, primary renal diagnosis, date and cause of death.[12] No information regarding (chemo)therapy is provided.

Patients were divided into two cohorts based on the initial date of dialysis treatment: a pre-guideline cohort (preGC)(January 1, 2002, until March 29, 2010) and post-guideline cohort (postGC)(March 29, 2010, until January 1, 2016). For our primary analysis we considered only the first change in renal status (dialysis independence, renal transplantation, death, remaining dialysis dependent). Additional changes were used for secondary analyses.

Dialysis independence was defined as restoration of renal function leading to dialysis independence for at least two consecutive months.[13] Restoration of renal function as a result of renal transplantation was classified as failure to achieve dialysis independence by the use of bortezomib. For comparison purposes, maximum follow up was limited to 4 years for each patient.

The primary endpoint was dialysis independence, depicted using the Kaplan-Meier method. Cox proportional hazards modeling was used to assess pre- and post-guideline differences. Adjusted hazard ratios (HRadj.) with 95% confidence intervals (95%CI) were estimated using a multivariable model. All indicators univariately associated (P<0.10) with achieving dialysis independence were considered for multivariable modeling. A two-tailed P value <0.05 indicated statistical significance. Analyses were performed using Statistical Analysis System version 9.4 (SAS Institute, Cary, NC, USA).

During the study period, 710 patients were registered in Renine. Ten patients were excluded due to immediate renal transplantation (n=2) or loss of follow up after initial registration in Renine (n=8). The baseline characteristics are presented in Table 1. The preGC and postGC consisted of 422 and 278 patients, respectively. There were no significant differences regarding gender, age, type of dialysis, or primary renal disease between the cohorts.

As Figure 1 shows, 19% (n=43) of the patients became dialysis independent in the postGC compared to 11% (n=32) in the preGC within 4 years after starting dialysis treatment. Median follow up in the preGC and postGC was 1.3 years [95%CI 1.1-1.6] and 1.2 years [95%CI 0.9-1.4], respectively. Dialysis independence was mainly reached in the first year of dialysis treatment, during which more patients became independent more rapidly in the postGC. Within the first year, the postGC showed a 2.3-fold increased chance of becoming dialysis independent ($HR_{adj.}$≤1year=2.3 [95%CI 1.5-4.0]), whereas

Table 1. Baseline characteristics of the Dutch MM population on renal replacement therapy.

	Total (n = 700)		Pre-guideline (n = 422)		Post-guideline (n = 278)		*P*
Male sex; n (%)	412	(59)	246	(58)	166	(60)	0.75
Mean age; years (SD)	66	(12)	65	(11)	66	(12)	0.44
Age; n (%)							0.28
< 65	289	(41)	180	(43)	109	(39)	
65 – 75	256	(37)	157	(37)	99	(36)	
≥ 75	155	(22)	85	(20)	70	(25)	
Type of dialysis; n (%)							0.30
Hemodialyses	613	(88)	365	(86)	248	(89)	
Peritoneal dialysis	87	(12)	57	(14)	30	(11)	
Primary renal disease; n (%)							0.14
MM nephropathy	478	(68)	279	(66)	199	(72)	
AL amyloidosis	222	(32)	143	(34)	79	(28)	

P values indicate differences between the pre- and post-guideline cohort. MM: multiple myeloma; AL: amyloidosis: amyloid light chain amyloidosis.

Table 2. Hazard ratios for achieving *Dialysis Independence* within 4 years in univariate and multivariable analyses of MM patients.

Risk factors	Univariate analysis Crude HR (95% CI)		P	Multivariable analysis Adjusted HR (95% CI)		P
Sex			0.533	–		
Female	1					
Male	1.2	(0.70 – 1.9)				
Age			0.059			0.040
< 75 years	2.0	(0.97 – 3.9)		2.1	(1.0 – 4.2)	
≥ 75 years	1			1		
Primary renal disease			< 0.001			< 0.001
AL amyloidosis	1			1		
MM nephropathy	6.0	(2.6 – 13.8)		5.7	(2.5 – 13.2)	
Type of dialysis			0.038	–		
Peritoneal dialysis	1					
Hemodialysis	2.9	(1.1 – 7.9)				
Treatment*						
Pre-guideline ≤ 1 year	1		< 0.001	1		< 0.001
Post-guideline ≤ 1 year	2.5	(1.5 – 4.0)		2.3	(1.4 – 3.7)	
Pre-guideline > 1 year	1		0.949	1		0.826
Post-guideline >1 year	0.95	(0.18 – 5.0)		0.83	(0.16 – 4.4)	

*Treatment according to the guideline analyzed as initial response within the first year of dialysis dependence versus the response after one year of dialysis dependence (time dependent variable in Cox regression). MM: multiple myeloma, AL: amyloidosis: amyloid light chain amyloidosis.

after 1 year such a difference was no longer present ($HR_{adj.}$>1year=0.83 [95%CI 0.16-4.4]).

A substantial number of patients not reaching dialysis independence deceased. Median overall survival (OS) of patients on dialysis treatment was 1.32 years (95%CI 1.10-1.58) and 1.74 years (95%CI 1.39-2.21) for the preGC and postGC, respectively (*Online Supplementary Figure S2*).

In addition to treatment period, multivariable modeling showed a significantly better outcome for patients <75 years compared to the older patients ($HR_{adj.}$=2.1 [95%CI 1.0-4.2], Table 2). There was no difference between patients aged <65 and 65-75 years (HR=1.0 [95%CI 0.6-1.7]). Therefore, age was included as <75 *vs.* ≥75 years. Patients with MM nephropathy (MCN or LCDD) were almost 6 times more likely to reach dialysis independence than patients with AL amyloidosis (HRadj.=5.7 [95%CI 2.5-13.2]). Gender and type of dialysis were not significantly associated with achieving dialysis independence.

Of the 75 patients who became dialysis independent, 16 (21%) eventually resumed dialysis within 4 years. The majority relapsed within 2 years. There was no significant difference in relapse between the two cohorts (HR=0.84 [95% CI 0.31-2.2]; *Online Supplementary Figure S3*).

This is one of the largest studies of MM patients with dialysis dependency to date, encompassing all MM patients on dialysis in the Netherlands over a period of 14 years. The number of patients becoming independent of dialysis doubled after establishing bortezomib as first-line treatment in MM patients with RI, independent of other risk indicators. This difference was mainly observed in the first year of dialysis treatment.

Our study underlines the poor prognosis in the restoration of renal function once a MM patient is dialysis dependent. Loss of dialysis independence was not significantly different before or after 2010, indicating that the improved probability of dialysis independence was not caused by a higher risk of relapse but rather a sustained response to therapy. In line with the OS of previous studies, OS of patients who remained on dialysis was poor in both cohorts.[10,11] As found by others,[10] our study showed that patients with MM nephropathy were almost 6 times more likely to become dialysis independent than patients with AL amyloidosis. This may be explained by the etiology of AL amyloidosis, where fibrils are mainly deposited in the glomeruli and soft tissues, as opposed to the possibly more reversible nature of MCN and LCDD where no fibrils are formed.

The improvement in dialysis independence after the introduction of bortezomib was previously suggested in France. Decourt *et al.*[10] used the national database REIN and after 2 years of follow up, 5% of the patients became dialysis independent between 2002-2006 compared to 13% between 2006-2011. However, the coverage of patients in this period was not 100%[14] and selection bias could have occurred. The lower percentages in the French study could be explained as bortezomib was not yet used as a first-line treatment in 2006 in France and the exposure of bortezomib in our patients could therefore be higher and earlier in the course of the disease. In addition, in a second French study,[11] dialysis independency of 17% and 44% was observed after 2 years in the preGC (1999-2008) and postGC (2008-2014), respectively. However, this was a small, single-center study and patients with AL amyloidosis were excluded.

The major strength of our study is the compulsory nature, quality, and completeness of the collected information in Renine. The database provides a representative, population-based, and complete overview of dialysis treatment in the Netherlands without selection bias

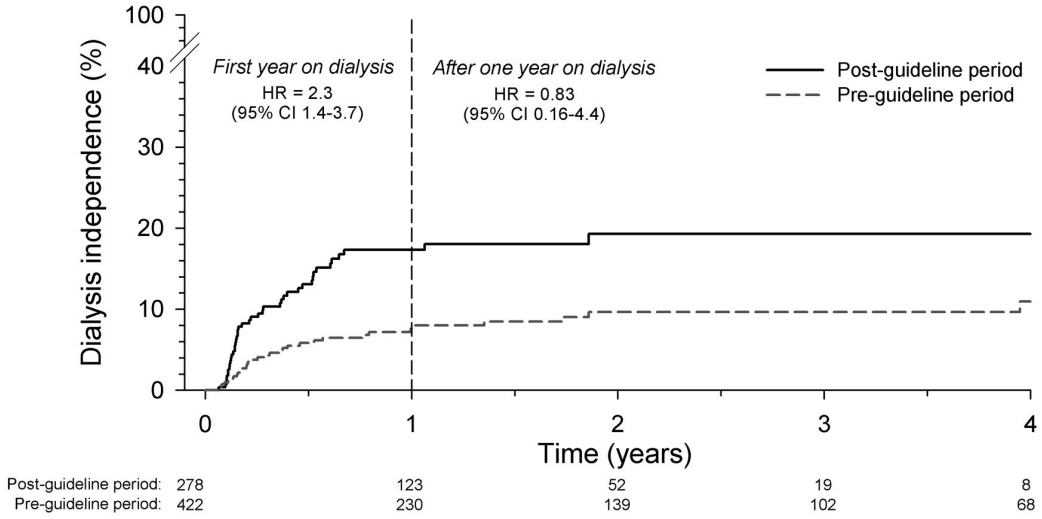

Figure 1. Percentage of patients achieving *Dialysis Independence* within 4 years after starting dialysis. Hazard ratios were derived from a time-dependent model in which the effect of treatment (pre- *vs.* post-guideline) was divided in an early-on effect and the effect after one year of dialysis dependence. A hazard ratio >1 indicates an increased 'risk' of achieving *Dialysis Independence* resulting from the post-guideline *versus* the pre-guideline treatment.

and with a long follow up. However, this study had some limitations. Firstly, no detailed information about MM disease history or treatment was recorded. Therefore, the phase at which dialysis was needed or the use of bortezomib was unknown for individual cases. As bortezomib was prescribed as second- and/or third-line treatment at progression or relapse and was administered off-label as induction therapy in MM patients with RI before 2010, we speculate that the effect of bortezomib on renal recovery is likely to be even more prominent than presented here. Furthermore, we recently showed that the majority of MM patients with an eGFR below 15 ml/min received a bortezomib-based treatment as first-line treatment in the last decade.[15] Secondly, renal biopsies were only routinely performed to confirm AL amyloidosis. The exact etiology of nephropathy due to MM may be unknown and could induce bias. Thirdly, improved care could have influenced the increase of achieving dialysis independence. Although unknown for patients in the Netherlands, Decourt *et al*. showed that control patients on dialysis without MM did not show an improvement in renal recovery before or after 2006.[10]

As illustrated by the poor OS, further steps are necessary to improve outcomes in patients on dialysis treatment. Our results showed that especially in the first year of dialysis treatment, restoration of renal function can be achieved. Therefore, a close interaction between nephrologists and haematologists in the diagnostic process, rapid initiation of more intensive therapy schemes comprising additional antimyeloma agents, and closer adherence to guidelines may be effective strategies to optimize outcomes in these patients.

In conclusion, our study showed an increase in the number of patients becoming independent of dialysis after the establishment of bortezomib as first-line treatment of MM patients with RI. This effect arises predominantly in the first year of dialysis treatment. Age <75 years and MCN/LCDD as primary renal disease were associated with achieving dialysis independence.

Berdien E. Oortgiesen,[1] Roshna Azad,[1] Marc H. Hemmelder,[2] Robby E. Kibbelaar,[3] Nic J.G.M. Veeger,[4,5] Joost C. de Vries,[6] Eric N. van Roon,[1,7,#] and Mels Hoogendoorn[6,#]

[1]Department of Clinical Pharmacy and Pharmacology, Medical Center Leeuwarden; [2]Department of Nephrology, Medical Center Leeuwarden; [3]Department of Pathology, Pathology Friesland, Leeuwarden; [4]Department of Epidemiology, MCL Academy, Leeuwarden; [5]Department of Epidemiology, University of Groningen, University Medical Center Groningen; [6]Department of Hematology, Medical Center Leeuwarden and [7]Unit of Pharmacotherapy, Epidemiology and Economics, Department of Pharmacy, University of Groningen, the Netherlands

[#]These authors share senior authorship.

Acknowledgments: the authors like to thank the Nefrovisie Foundation as owner of Renine for providing the data and for giving us permission to use the data for scientific purposes.

Correspondence: Berdien.Oortgiesen@znb.nl.

doi:10.3324/haematol.2017.184754

Information on authorship, contributions, and financial & other disclosures was provided by the authors and is available with the online version of this article at www.haematologica.org.

References

1. Dimopoulos MA, Terpos E, Chanan-Khan A, et al. Renal impairment in patients with multiple myeloma: a consensus statement on behalf of the International Myeloma Working Group J Clin Oncol. 2010;28(33):4976-4984.
2. San-Miguel JF, Richardson PG, Sonneveld P, et al. Efficacy and safety of bortezomib in patients with renal impairment: results from the APEX phase 3 study Leukemia. 2008;22(4):842-849.
3. Dimopoulos MA, Roussou M, Gkotzamanidou M, et al. The role of novel agents on the reversibility of renal impairment in newly diagnosed symptomatic patients with multiple myeloma Leukemia. 2013;27(2):423-429.
4. Sonneveld P, Zweegman S, Vellenga E, Wittebol S, Sinnige H, Meijer E. Guidelines for treatment of plasma cell dyscrasias in 2010 Ned Tijdschr Hematol. 2010;7:84-94.
5. Tsakiris DJ, Stel VS, Finne P, et al. Incidence and outcome of patients starting renal replacement therapy for end-stage renal disease due to multiple myeloma or light-chain deposit disease: an ERA-EDTA

Registry study Nephrol Dial Transplant. 2010;25(4):1200-1206.
6. Evison F, Sangha J, Yadav P, et al. A population-based study of the impact of dialysis on mortality in multiple myeloma Br J Haematol. 2018;180(4):588-591.
7. Dimopoulos MA, Sonneveld P, Leung N, et al. Dimopoulos MA, Sonneveld P, Leung N, et al. International Myeloma Working Group recommendations for the diagnosis and management of myeloma-related renal impairment J Clin Oncol. 2016;34(13):1544-155.
8. Torra R, Blade J, Cases A, et al. Patients with multiple myeloma requiring long-term dialysis: presenting features, response to therapy, and outcome in a series of 20 cases Br J Haematol. 1995;91(4):854-859.
9. Dimopoulos MA, Kastritis E, Rosinol L, Blade J, Ludwig H. Pathogenesis and treatment of renal failure in multiple myeloma Leukemia. 2008;22(8):1485-1493.
10. Decourt A, Gondouin B, Delaroziere JC, et al. Trends in survival and renal recovery in patients with multiple myeloma or light-chain amyloidosis on chronic dialysis Clin J Am Soc Nephrol. 2016;11(3):431-441.
11. Laforet M, Jourde-Chiche N, Haddad F, et al. Evolution in the treatment of multiple myeloma and impact on dialysis independence: data from a French cohort from 1999 to 2014 Blood Cancer J. 2016;6:e409.
12. Renine, Dutch Renal Replacement Registry, the Nefrovisie foundation, Utrecht, the Netherlands [Internet]. Available from: http://www.nefrovisie.nl/renine/.
13. Dimopoulos MA, Roussou M, Gavriatopoulou M, et al. Reversibility of renal impairment in patients with multiple myeloma treated with bortezomib-based regimens: identification of predictive factors Clin Lymphoma Myeloma. 2009;9(4):302-306.
14. Couchoud C, Stengel B, Landais P, et al. The renal epidemiology and information network (REIN): a new registry for end-stage renal disease in France Nephrol Dial Transplant. 2006;21(2):411-418.
15. de Vries JC, Oortgiesen B, Hemmelder MH, et al. Restoration of renal function in patients with newly diagnosed multiple myeloma is not associated with improved survival: a population-based study Leuk Lymphoma. 2017;58(9):1-9.